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UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE INCORPORATED, Plaintiff, v. VYSIS, INC., Defendant.	No. 99CV2668H AJB **PLAINTIFF GEN-PROBE INCORPORATED'S REPLY MEMORANDUM OF POINTS AND AUTHORITIES IN SUPPORT OF ITS MOTION FOR PARTIAL SUMMARY JUDGMENT OF NON-INFRINGEMENT UNDER THE DOCTRINE OF EQUIVALENTS** Date: November 19, 2001 Time: 10:30 a.m. Dept: Courtroom 1

I.
THE ISSUE PRESENTED BY GEN-PROBE'S MOTION IS A QUESTION OF LAW

A device that does not literally infringe a patent claim may nonetheless infringe under the doctrine of equivalents only if every element is equivalently present in the accused device. *Sage Products, Inc. v. Devon*, 126 F.3d 1420, 1423 (Fed. Cir 1997). A product or process that does literally infringe is an "equivalent" only if it has *insubstantial* differences from the corresponding element in the claims. *Id.*

There can be no infringement under the doctrine of equivalents if such a finding would effectively eliminate *any* individual element in a patent claim. *Warner-Jenkinson Co. v. Hilton*

Davis Chemical Co., 520 U.S. 17, 39 n. 8 (1997). In considering the "equivalence" of an accused method, claim definitions and limitations that are implicit must be considered to the same extent as claim definitions and limitations that are express. *Id.*

The issue of whether a reasonable jury could find equivalence or whether equivalence would vitiate a claim element, express or implied, is a question of law for the Court. The Court should grant summary judgment in any case where a finding of equivalence is precluded on either ground. *Sage Products,* 126 F.3d at 1423.

II.
THE UNDISPUTED EVIDENCE ESTABLISHES SUBSTANTIAL DIFFERENCES BETWEEN "TMA" AND THE NON-SPECIFIC AMPLIFICATION METHODS OF THE '338 PATENT

While Vysis has submitted significant argument to the Court, in the end this motion must be decided on the basis of the evidence, *e.g.*, the undisputed facts, and not on the basis of mere argument.

Therefore, the most significant document on this motion is Gen-Probe's Separate Statement of Undisputed Facts, and Vysis' supplemental response to that statement. The 27 pages of argument submitted by Vysis in two opposition briefs is significantly less probative. Almost all of the relevant facts are undisputed.

In response to Gen-Probe's May 2001 motion on the issue of literal infringement, Vysis admitted the following important facts:

- Gen-Probe's HIV/HCV assay uses a target-specific amplification technology called Transcription Mediated Amplification (TMA). (May 25, 2001 "Defendant's Statement of Disputed Facts In Opposition To Plaintiff's Motion for Partial Summary Judgment," Fact No. 26.)
- TMA uses specific primers, specific promoters, and a specific polymerase enzyme that recognizes only those promoters. (*Id.*, Fact No. 27.)
- Gen-Probe's product does not use non-specific amplification. (Id., Fact No. 28.)

In response to the Separate Statement submitted in support of this motion, Vysis has unconditionally admitted the following additional facts:

- Gen-Probe's TMA method functions to exponentially increase both the ***absolute*** and ***relative*** amount of a particular nucleic acid sequence of interest in a mixture of nucleic acids. (November 8, 2001 "Defendant's Supplemental Statement of Disputed Facts In

Opposition To Plaintiff's Motion for Partial Summary Judgment of Non-infringement Under the Doctrine of Equivalents," Fact No. 5.)

- When a particular nucleic acid sequence of interest is contained in a mixture of nucleic acids in a clinical sample, TMA enables a person skilled in the art to exponentially copy the sequence of interest. (*Id.*, Fact No. 8.)
- This makes it easy to determine whether or not a pathogenic microorganism is hiding among millions of other organisms in a patient sample. (*Id.*, Fact No. 9.)
- The enzymes and primers used in any amplification process can be specific or non-specific. (*Id.*, Fact No. 12.)
- The primers used in Gen-Probe's specific TMA amplification method have been carefully selected by Gen-Probe's scientists and are generally designed to bind to specific, unique sequences in a DNA or RNA molecule. (*Id.*, Fact No. 13.)
- By contrast, non-specific primers and enzymes will amplify *any* and *all* sequences present in the sample. (*Id.*, Fact No. 17.)
- The random primers used in non-specific amplification will bind to all of the sequences in the sample and non-specific replication enzymes will catalyze DNA synthesis at points throughout the entire lengths of the nucleic acid molecules present without regard to sequence. (*Id.*, Fact No. 18.)
- In its TMA method, Gen-Probe uses two amplification enzymes that depend upon the presence of specific primers. (*Id.*, Fact No. 19.)
- One of these enzymes is reverse transcriptase ("RT"). (*Id.*, Fact No. 20.)
- RT is a DNA polymerase that produces a complementary DNA strand copy of a single-stranded RNA or DNA that has a bound primer. (*Id.*, Fact No. 21.)
- In TMA, RT produces complementary DNA from the target nucleic acids (or their complementary strands) only if the sequence-specific primers first bind to a single strand of RNA or DNA. (*Id.*, Fact No. 22.)
- Another specific primer used in Gen-Probe's method also includes a specific "promoter" sequence that is recognized by another enzyme ("T7 RNA polymerase") that binds specifically to that promoter sequence to produce many RNA copies by transcription. (*Id.*, Fact No. 24.)
- If the double-stranded, and hence functional, T7 promoter used in TMA *is* formed as a result of these *two* primer binding and extension processes, then the T7 RNA polymerase used in Gen-Probe's HIV/HCV test will amplify the sequence attached to the T7 promoter sequence. (*Id.*, Fact No. 26.)
- In contrast to the exponential amplification achieved by TMA, the non-specific amplification methods of Examples 4 and 5 of the '338 patent admittedly achieve only linear amplification, not exponential amplification. (*Id.*, Fact No. 34.)
- Non-specific amplification using random hexamer primers results in fragmented nucleic acids, each of which contains the random sequences present in the primers. (*Id.*, Fact No. 38.)

- PCR was well known to the inventors and the scientific community at large. Dr. Kary Mullis invented PCR in 1983, for which he received the Nobel Prize in Chemistry. Dr. Mullis and his colleagues publicly described PCR at a scientific meeting in the summer of 1985 and published their discovery in December 20, 1985. (*Id.*, Fact No. 45.)

- James Richards, Gene Trak's Director of Business Development and Licensing, admits that, within the scientific community, PCR was immediately "big news." (*Id.*, Fact No. 46.)

- One of the reasons that the '338 inventors sought to find something "different" from specific amplification techniques such as PCR was due to Gene Trak's concern that it could not obtain a license from Cetus Corp. to use PCR. Cetus Corporation, which employed Dr. Mullis, originally owned the rights to PCR. Gene-Trak sought a license from Cetus, but its requests were rejected. (*Id.*, Fact No. 47.)

All of these facts are undisputed. These admitted facts alone would require that Gen-Probe's motion be granted.

However, additional facts can be found to be undisputed as a matter of law. For example, Vysis "disputes" the facts set forth below, but has failed to cite any evidence at all to demonstrate a *bona fide* disputed. Gen-Probe has provided evidence in support of each of these facts, and the facts are undisputed as a matter of law by Vysis' failure to cite evidence in its response. The following facts are undisputed on this basis:

- Vysis' expert, Dr. Persing, has admitted that "without the invention [i.e., the combination of a preliminary "target capture" step with amplification], ***only specific amplification could be used***." (*Id.*, Fact No. 11.)

- If the products of one round of non-specific amplification were subjected to another round of non-specific amplification, the resulting products would be smaller still. (*Id.*, Fact No. 36.)

- The resulting products of nonspecific amplification with random hexamer primers are heterogeneous and have undefined composition. (*Id.*, Fact No. 39.)

- The Court has previously noted that the specification of the '338 patent contains no reference to any specific amplification techniques. To the contrary, the specification clearly suggests that the claimed amplification techniques of the invention don't require the use of specific primers necessary for specific amplification. (*Id.*, Fact No. 42.)

- The absence in the '338 patent of any disclosure of specific amplification techniques was not accidental or unintended. To the contrary, Gene-Trak Systems, Vysis' predecessor-in-interest, and its employed inventors were well aware of the specific amplification techniques such as PCR. In fact, the admitted focus of the inventors' effort leading to the disclosure in the '338 patent was to find something "different" from specific amplification. For example, inventor Jon Lawrie testified that the patent was meant to cover *new* amplification methods using non-specific primers, not already-known methods such as PCR . (*Id.*, Fact No. 43.)

- Inventor King also stated the inventors' was to find amplification methods ***that did not involve PCR amplification***. (*Id.*, Fact No. 44.)

- Dr. Richards of Gene-Trak pointedly contrasted the '338 patent's method of non-specific amplification with other known specific methods that used specific primers or promoters and stated that methods that used specific primers were "*the opposite" of* non-specific primer or promoters as claimed in the '338 patent. (*Id.*, Fact No. 43.)

Further, Vysis disputes additional facts only on the legally-incorrect argument that the results of non-specific amplification may be considered "in the context of the invention." This response is legally insufficient to establish a triable issue of disputed fact in light of the Supreme Court's express instruction that "[T]he doctrine of equivalents must be applied to the individual elements of the claim, not to the invention as a whole." *Warner-Jenkinson Co.*, *supra*, 520 U.S. at 29. Infringement cannot be proved by showing that an accused devise or process is equivalent "overall." *Id.*; a*ccord, Gamma-Metrics Inc. v. Scantech Ltd.*, 52 USPQ2d 1568, 1574 (S.D. Cal. 1998) (Huff, J.) The Supreme Court's decision in *Warner-Jenkinson* eliminated the "consider the entire invention" argument now relied on by Vysis.

The facts which Vysis disputes only on the basis of the legally-insufficient "context of the invention" argument are:

- In direct contrast to specific amplification methods which increase both the relative and absolute amount of the target nucleic, non-specific amplification functions only to increase the absolute amount of *all* nucleic acids present in a sample and does ***not*** increase the relative amount of a particular nucleic acid sequence of interest. (November 8, 2001 "Defendant's Supplemental Statement of Disputed Facts In Opposition To Plaintiff's Motion for Partial Summary Judgment of Non-infringement Under the Doctrine of Equivalents," Fact No. 6.)

- Specific amplification is useful for diagnostic purposes even without a target capture step. In contrast, non-specific amplification is *not* a viable diagnostic method because it does not increase the amount of a target nucleic acid relative to everything else. Vysis' own expert witness has admitted this important distinction: "Without the use of target capture prior to amplification, ***non-specific amplification would not be a viable technique for detecting target nucleic acids in a sample*** because, as pointed out in the quoted paragraph, non-specific amplification causes the replication of virtually any nucleic acid sequence, including other irrelevant nucleic acids in the sample." (*Id.*, Fact No. 10.)

Finally, Vysis disputes a number of facts only on the basis that "all nucleic acid

amplification techniques have some degree of nonspecificity." (*Id.*, Fact Nos. 16, 23, 25, 27, 28, 29, 30, 37, and 40.) However, Gen-Probe has submitted the Reply Declaration of Kary Mullis, the inventor or PCR, that establishes that non-specific products do not change the sequence-specific nature of PCR and TMA. Further, Vysis' own expert is the author of numerous articles that support this position:

> In general, the specifically amplified target sequence is the predominant amplification product and is easily identified by its precisely identified length; nonspecific amplification products tend to be heterogeneous ins ize, and they do not usually become the predominant product.

D. Persing, M. Landry, "*In Vitro* Amplification Techniques for the Detection of Nucleic Acids: New Tools for the Diagnostic Laboratory," Yale J. Biology and Medicine 62: 159, 162 (1989).

> [The product of PCR] is identified by its precisely defined length and the presence of internal target sequences. Nonspecific amplification products (that is, spuriously amplified sequences that do not contain the specific target sequence) are only rarely the same size as the target-specific product and do not contain internal sequences that are homologous to target-specific hybridization probes.

D. Persing, "*In Vitro* Nucleic Acid Amplification Techniques," Diagnostic Molecular Microbiology, at 58 (Persing et al., eds. 1993)

> If only 90% of the targets are extended in each cycle, 20 cycles would yield a 375,000 fold amplification. Nontarget sequences that anneal to one primer and become extended could at most increase 20-fold in concentration during 20 cycles because the product of the first primer extension is not likely to contain the sequence region complementary to the other primer.

T. White, R. Mandej, D. Persing, "The Polymerase Chain Reaction: Clinical Applications," Advances in Clinical Chemistry 29: 161, 164 (1992). The fact that TMA may have some degree of non-specific byproducts does not make it the equivalent of nonspecific amplification with random hexamer primers and non-specific enzymes. Gen-Probe has obtained FDA approval of two TMA tests that do not include a target step. (Persing Depo. at 30:8-12; 79-81.) These assays

have a clinical specificity of 100% and 99%, respectively. Y. Tang, G. Procop, and D. Persing, "Molecular Diagnostics of Infectious Diseases," Clinical Chemistry 43: 11: 2021, 2028 (1997).

Taken together, all of the facts are either undisputed by Vysis, disputed on legally-invalid grounds, or disputed on a factually immaterial basis. It is clear why Vysis previously sought entry of judgment on the issue of non-infringement and stated that it could not prevail on the issue. The undisputed facts before the Court establish that TMA is substantially different from non-specific amplification with random hexamer primers and that the two methods *do not* perform substantially the same function in substantially the same way to achieve substantially the same result.

III.
VYSIS' RELIANCE ON EXAMPLE 5 IS MISPLACED

Just as it did in connection with the prior motion on the issue of literal infringement, Vysis continues to argue that Example 5 of the '338 patent discloses specific amplification, and that therefore the method of Example 5 is "equivalent" to TMA. The Court properly rejected this argument on the last motion and the argument deserves no more merit when asserted as proof of equivalence. Inventor Lawrie said Example 5 disclosed non-specific amplification:

> Q. So Example 5 discloses a linear nonspecific method of amplification?
>
> A. Yes.

Lawrie Depo. at 231: 4-6. Inventor Halbert said the same thing:

> Q. At least as to the four -- the Examples 4 through 7, is there any information or reference with respect to those examples that you would characterize to suggest specific amplification?
>
> A. To suggest specific amplification?
>
> Q. Yes.
>
> A. Not to my knowledge.

Halbert Depo. at 94: 1-7. Example 5 itself describes the process as nonspecific. Vysis' own expert witness, David Persing, was unable to state whether Example 5 resulted in specific or non

specific amplification. (Persing Depo. at 97:22-98:7; 99:16-23; 114:20-24.) Vysis' reliance on Example 5 is misplaced.

IV.
VYSIS HAS FAILED TO PROPERLY SEEK RECONSIDERATION

The argument directed to Example 5 on the issue of equivalence is nothing more than a *de facto* motion for reconsideration of the Court's prior ruling. In fact, the greatest part of Vysis' original and supplemental opposition papers address the Court's prior ruling rather than the instant motion. Vysis has failed to comply procedurally or substantively with the requirements for a motion for reconsideration. Gen-Probe is precluded by time and page limitations from now responding to all of the arguments made by Vysis with respect to the prior order. (The accompanying declaration of Kary Mullis strongly supports the Court's original ruling.)

Vysis contends that the Court improperly read into the claims a limitation from the specification. Vysis cites to *Dayco Prods., Inc. v. Total Containment, Inc.*, 258 F.3d 1317, 1327 (Fed. Cir. 2001); *Gart v. Logitech, Inc.*, 254 F.3d 1334 (Fed. Cir. 2001); and *Interactive Gift Express, Inc. v. Compuserve Inc.*, 256 F.3d 1323 (Fed. Cir. 2001) and argues that these cases provide "ongoing clarification of the applicable law" of the Federal Circuit. Opp. at 7:11-13. Each of these cases involves a situation where the Federal Circuit reversed a claim construction on the basis that the district court improperly read a limitation from the specification into the construed claim. However, nothing about the holdings of these cases provides any basis for the Court to reconsider its construction of the term "amplifying." This Court did not read a limitation from the specification into the claim and, hence, the rulings from these cases are inapt.

Even Vysis cannot reasonably dispute that the "[c]laims must be read in view of the specification, of which they are a part." *Markman v. Westview Instruments, Inc.* 52 F.3d 967, 979 (Fed. Cir. 1995), *aff'd*, 517 U.S. 370 (1996). Claims may not be validly construed to be broader than the supporting disclosures of the specification. *Gentry Gallery, Inc. v. Berkline Corp.*, 134 F.3d 1473, 1479-80 (Fed. Cir. 1998). The Court properly construed the term "amplifying" based on the teachings set forth in the specification of the '338 patent.

The Federal Circuit has made clear that although the specification of a patent need not

present every embodiment of the invention and the claims are not limited to the preferred embodiment of the invention, the claims can not enlarge what is patented beyond what the inventor has described as the invention. *See Wang Laboratories, Inc. v. America Online, Inc.*, 197 F.3d 1377, 1383 (Fed. Cir. 1999); *SciMed Systems, Inc. v. Advanced Cardiovascular Systems, Inc.*, 242 F.3d 1337, 1341 (Fed. Cir. 2001). As this Court noted in its claim construction ruling,

> the specification of the '338 patent does not describe specific amplification methods and does not teach any benefits from the combination of target capture and specific amplification. In fact, the specification teaches that you do not need to do specific amplification. The specification refers to specially tailored primers only to state that they are not necessary when an initial target capture step is used.

Order at 7:20-24. "Where the specification makes clear that the invention does not include a particular feature, that feature is deemed to be outside the reach of the claims of the patent, even though the language of the claims, read without reference to the specification, might be considered broad enough to encompass the feature in question. *SciMed Systems, Inc. v. Advanced Cardiovascular Systems, Inc.*, 242 F.3d 1337, 1341 (Fed. Cir. 2001). Rather than "improperly reading" a limitation from the specification into the claim as Vysis contends, this Court properly construed the term "amplifying" to include only non-specific methods of amplification because that was consistent with the disclosures of the '338 patent. The Court's ruling is entirely consistent with the decisions of the Federal Circuit mandating that claim terms must be determined to be consistent in scope with the disclosures of the specification. *See, e.g., Wang Laboratories, Inc. v. America Online, Inc.*, 197 F.3d 1377 (Fed. Cir. 1999); *SciMed Life Systems, Inc. v. Advanced Cardiovascular Systems, Inc.*, 242 F.3d 1337 (Fed. Cir. 2001); *O.I. Corp v. Tekmar Co.*, 115 F.3d 1576 (Fed. Cir. 1997); *Kraft Foods, Inc. v. International Trading Co.*, 203 F.3d 1362 (Fed. Cir. 2000); *Toro Co. v. White Consolidated Industries, Inc.* 199 F.3d 1295 (Fed. Cir. 1999).

V.
CONCLUSION

By definition, a "non-specific" process cannot be the equivalent of a process that

admittedly uses sequence-specific primers, promoters, and enzymes, just as a metallic element -- by definition -- cannot, be the equivalent of a "non-metallic" element.

The undisputed facts establish that Gen-Probe's ATMA amplification method performs a different function, operates in a different way, and obtains a different result than the non-specific amplification methods claimed in the '338 patent. Therefore the differences between the two methods cannot be found to be "insubstantial," as would be required to establish equivalency. Summary judgment should be granted.

Dated: November 13, 2001

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